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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,333	11/14/2001	Larry Wayne Oberley	875.042US1	5690

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 09/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,333	OBERLEY ET AL.	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2003 and 06 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5-8,11-15 and 17-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *20 and 21* is/are allowed.

6)☒ Claim(s) *2, 3, 5, 6, 7, 8, 11-15, and 17-19 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date ~~10-11-2002~~ 10-30-03 10-21-2003
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on October 27, 2003 and July 6, 2004 have been entered.

Status of Application/Amendment/Claims

2. Applicant's response filed October 27, 2003 and July 6, 2004 has been considered. Rejections and/or objections not reiterated from the previous office action mailed April 21, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

3. The information disclosure statements (IDS) entered on October 24, 2002, and October 30, 2003 were filed before the mailing date of the first action following the Request for

Continued Examination referred to above. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner, and are enclosed herewith.

Response to Election/Restrictions

4. Applicant's arguments regarding the restriction requirement of June 2, 2004 are persuasive. Accordingly the restriction requirement of June 2, 2004 is hereby withdrawn. The requirement is withdrawn because, while the Groups listed in said restriction requirement are considered to be directed to patentably distinct subject matter, it is not considered a search burden to identify oligos targeting the start codons of all such targets as now claimed.

Response to Arguments, 35 U.S.C. § 112 first paragraph

5. Claims 2, 3, 5, 6, 7, 8, 11-15, and 17-19 and 22-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the same reasons of record as set forth in the Office action dated June 18, 2002.

Independent claim 6 recites:

> "An oligonucleotide comprising an antisense nucleic acid sequence that specifically binds to a nucleic acid encoding a human antioxidant enzyme start codon, wherein the antisense sequence is about 18 to 26 nucleotides in length, and wherein the antioxidant enzyme ..." is chosen from one of five different enzymes.

It is emphasized that, contrary to applicants indications, the claims as written embrace more than just antisense to any of the five recited antioxidant enzymes. Rather, as worded, the claims read

on an antisense oligo that targets any portion of any nucleic acid, so long as that nucleic acid encodes a human start codon that also happens to be found in any of the five recited human antioxidant enzymes.

Furthermore, the start codons of all five enzymes are not only identical to each other (see applicant's response of July 6, 2004 at page 9, 2nd paragraph), but also to virtually every other known start codon in general. It is well known in the art that most all start codons of a given mRNA comprise an AUG nucleotide motif that is very highly conserved across most every gene and species with very few exceptions (see attached photocopy from page 121 of Molecular Biology of the Cell, 3rd Ed., 1995, Darnell *et al.*, Scientific American Books, NY, New York, where it is stated that "The 'start' (initiator) codon AUG specifies the amino acid methionine: all protein chains in prokaryotic and eukaryotic cells begin with this amino acid") . Thus it is maintained that the claim language encompasses any antisense targeted to most any RNA target, across most any species, so long as the nucleotide sequence contains the highly ubiquitous AUG start codon motif.

Applicants have traversed the instant rejection by pointing to the claim amendments that now require the start codons to be of human origin. However, as pointed out above, the consensus start codon motif of AUG/ATG is shared not only by the instantly recited five antioxidant mRNA transcripts, but also by most humans and non-human genes. Accordingly, the amendment to insert the term "human" into the claims is not considered sufficient to overcome the instant rejection.

Furthermore, even if the claims were amended to claim only those antisense oligos that are directed to any of the five recited human antioxidant enzymes, this would not be considered

sufficient to overcome the instant written description rejection. While applicants have provided the sequence of manganese superoxide dismutase in the form of SEQ ID NO: 11 in the specification, and have subsequently pointed to GenBank accession numbers X02317, M21304, and AF199441 as teaching the sequences for copper and zinc superoxide dismutase and cytosolic glutathione peroxidase, this submission is not considered to provide adequate support for claims drawn to the broad genus of any such human target, because one of skill could not be apprised as to what structures present in these sequences allow one of skill to distinguish between a nucleic acid encoding a human antioxidant enzyme versus one that codes for a non-human version.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof.

Neither the teaching of SEQ ID NO: 11 of specification nor the submission of the accession numbers of the prior art referred to above are considered to provide sufficient distinguishing identifying characteristics of the genus of human antioxidant targets, because no accompanying description points out what structure/function relationship exists that would allow

one of skill to determine whether that a nucleic acid sequence is indeed human. Therefore, one of skill in the art could not envision the antisense targets that belong to the genus of human manganese superoxide dismutase, copper and zinc superoxide dismutase, catalase, phospholipid glutathione peroxidase, or cytosolic glutathione peroxidase as claimed, beyond those sequences provided. Accordingly, applicants are not considered to be in possession of the genus antisense oligos to said targets as now broadly claimed.

6. Claims 8, 11-15, and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vivo* antisense-mediated inhibition of human superoxide dismutase in the treatment of tumors, does not reasonably provide enablement for treatment of any tumor, for the same reasons of record as set forth in the Office action mailed June 18, 2002. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants have directed attention to the allegedly detailed description that applicants assert support enablement. Applicants argue that the specification teaches how to make oligos targeting any of the five antioxidant enzyme start codons, and that the specification exemplifies such oligos targeting catalase and cytosolic glutathione peroxidase mRNA, and further argues that methods of using a candidate oligo in *in vitro* has been exemplified successfully showing a reduction in the expression of that antioxidant.

No disagreement is found in regards to the evidence cited by applicants; however, their pertinence the instant rejection is disputed. For example, it is agreed that the specification

teaches specific oligos targeting manganese superoxide dismutase, catalase and cytosolic glutathione peroxidase, and that one of these oligos has been shown to work *in vitro*. This much has been conceded during prosecution. In fact in the preamble of this rejection, it is noted that applicants are considered enabled for *in vivo* inhibition of tumor growth using oligos targeted to manganese superoxide dismutase, as evidenced by the specification's exemplification of a reduction in tumor growth following administration of oligos targeted to manganese superoxide dismutase.

However, the scope of the claims is drawn to using any antisense oligo that targets any nucleic acid encoding a start codon from one of the five human antioxidant proteins recited in the claims. As explained above, this breadth is considered extraordinary, because the start codon of the five human antioxidant enzymes recited is the same start codon shared by virtually all genes across virtually all species. Furthermore, as first discussed in the action mailed June 18, 2002, the art of antisense mediated therapy is considered highly unpredictable, subject to such unresolved problems such as access to sites within the mRNA transcript to target, getting enough of the oligo inside the intended target cell to achieve target inhibition, and finally, actually verifying that inhibition of the target results in treatment of the disease as claimed. Although applicants have disclosed one oligo that may achieve gene inhibition in a xenograft model, this does not provide any indication whether any other oligo is capable of ever achieving *in vivo* treatment, particularly in view of the well-known and problematic issues in the art of using antisense oligos to mediate the treatment of tumors *in vivo*. This is supported by statements from those of skill in the art, such as Tamm *et al.* (of record): until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent

predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach." The state of the art at the present time is such that the antisense sequence does not solely determine the therapeutic effect. Thus, it is maintained that while applicants have exemplified several antisense compounds, there is no predictability associated with their use in achieving *in vivo* therapeutic success.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 3, 5, 6, 7, and 22-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Gonzalez-Zulueta *et al.* (of record).

The invention of the above claims is drawn to "an oligonucleotide comprising an antisense nucleic acid sequence that specifically binds to a nucleic acid encoding a human antioxidant enzyme start codon," wherein the antioxidant enzyme is manganese superoxide dismutase, copper and zinc superoxide dismutase, catalase, phospholipid glutathione peroxidase, or cytosolic glutathione peroxidase, wherein the antisense compound is about 18 to 26 nucleotides, wherein said compounds may be phosphorothioated, or wherein the antisense compound ranges in length from about 18 to 26, or is about 20, and has sequence identity of 90% or 100%.

The claims, as written, embrace more than just antisense to any of the five recited antioxidant enzymes. Rather, as worded, the claims read on any antisense oligo so long as it targets any portion of any nucleic acid encodes a human start codon that is found in any of the five recited human antioxidant enzymes. Since it is well known in the art that human start codons are composed of an AUG/ATG nucleotide motif that is very highly conserved across most every gene and species with a few exceptions, and further because applicants acknowledge in their arguments at page 9 at the 2nd paragraph (applicant's response, July 6, 2004) that this motif is the start codon for each of the five antioxidant enzymes recited in the claims, it is maintained that the claim language encompasses antisense targeted to most any target, across most any species, so long as the sequence contains the AUG/ATG start codon motif.

Gonzalez-Zulueta et al. teach a phosphorothioated antisense compound targeted to a nucleic acid that encodes a human antioxidant enzyme start codon. Although the target of Gonzalez-Zulueta encodes a rat manganese superoxide dismutase (i.e. not human), the start codon is identical to the human start codon sequence. The oligo of Gonzalez Zulueta is 19 nucleotides long, which is considered to be about 20 nucleotides. Furthermore, because each of copper and zinc superoxide dismutase, catalase, phospholipid glutathione peroxidase, or cytosolic glutathione peroxidase all contain AUG/ATG "human" start codons, and because Gonzalez-Zulueta *et al.* teaches an antisense that targets a nucleic acid (i.e. manganese superoxide dismutase) that encodes this human start codon, Gonzalez-Zulueta is considered to anticipate compound claims reciting antisense to nucleic acids encoding the antioxidant enzymes.

Relevant Prior Art

8. The prior art of Sugino *et al.* Ferguson-Kohout *et al.*, Bauman *et al.*, and Baracchini *et al.*, all of record, are not relied upon but are considered pertinent to applicant's disclosure.

Allowable Subject Matter

9. Claims 20 and 21 are allowed, because the art does not teach or fairly suggest the sequence of SEQ ID NO: 2.

Conclusion

10. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

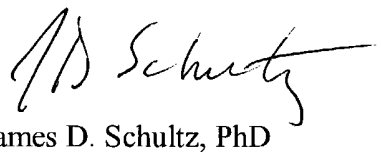
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete

service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JD Schultz, PhD



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